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Trade-offs and the evolution of virulence of microparasites: do details matter?

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Abstract

Models of the within-host dynamics of parasites have been used to consider the evolution of microparasites causing acute infections in vertebrate hosts. In this paper, we use these models to examine how the level of virulence to which a parasite evolves, depends on factors such as the relationship between parasite density and its rate of transmission from infected hosts, and the mechanism of parasite-induced pathogenesis. We show that changes in the terms describing transmissibility and pathogenesis may lead to dramatic differences in the level of virulence to which a parasite evolves. This suggests that no single factor is likely to be responsible for the differences in virulence of different parasites, and that understanding of the evolution of virulence of parasites will require a detailed quantitative understanding of the interaction between the parasite and its host.
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1. Introduction

Why are parasites[1] virulent? The adaptive model suggests that the level of virulence of a parasite is a consequence of its evolutionary adaptation to maximize its total transmission from infected hosts (Anderson and May, 1982). While we focus on this adaptive model, we note that there are alternatives—the virulence of some parasites may be coincidental (Bull, 1994; Levin and Bull, 1994; Ebert, 1999; Weiss, 2002), or may depend on the competition between different parasite strains within infected hosts (Frank, 1992; Bonhoeffer and Nowak, 1994; Nowak and May, 1994; May and Nowak, 1995; van Baalen and Sabelis, 1995).

The adaptive model can be understood in terms of the epidemiology of the infection, and in particular in terms of the basic reproductive number, R_0, of the infection caused by the parasite. R_0 is defined as the number of secondary infections produced by one infected host in a wholly susceptible population (Bremermann and Thieme, 1989; Anderson and May, 1991). In the adaptive model the parasite evolves to maximize its total transmission, and this is equivalent to maximizing R_0 (Bremermann and Thieme, 1989; Anderson and May, 1991). The R_0 of a directly transmitted infection can be written as

$$R_0 = \frac{\beta N}{b + \alpha + v}, \tag{1}$$

where β is the average transmissibility of the infection, α and b are the rate constants for the parasite-induced and natural host mortality, v is the rate of recovery from infection, and N is the density of susceptible hosts. The trade-offs between transmissibility β, host recovery rate v and virulence α determine the values of these parameters at which R_0 is maximum. The existence of some of these trade-offs is intuitive. For example, pathogens which cause infections with higher parasite densities might be expected to have higher transmissibility (β) and higher virulence (α), suggesting a positive correlation between transmissibility and virulence. However, experimental data on the functional form for these trade-offs is relatively limited (Fenner et al., 1956; Fenner and Ratcliffe, 1965; Anderson and May, 1982; Schulman, 1967; Mackinnon and Read, 1999).

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[1] We use the term parasites for microparasites such as viruses, bacteria, fungi, and protozoa, and focus on acute infections of vertebrate hosts.

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Models of the within-host dynamics of parasites have been used to understand how these trade-offs arise as a consequence of the interaction between the replicating parasite and the host immune response as well as the transmissibility of the parasite from the infected host (Sasaki and Iwasa, 1991; Antia et al., 1994; Ganusov et al., 2002; Gilchrist and Sasaki, 2002).

In Section 2 we briefly review a simple model for the within-host dynamics of microparasites causing acute infections in vertebrate hosts, and illustrate how this model can be used to understand the evolution of virulence of parasites (Ganusov et al., 2002). In the subsequent two sections we consider how the changes in some aspects of the interaction between the parasite and its host in the model affect the evolution of the parasite, and in particular how they affect the optimal level of virulence to which we expect the parasite to evolve. We consider two specific modifications to the initial model. In Section 3 we consider the consequences of changing the relationship between the within-host density of the parasite and its rate of transmission from a linear function to a saturating or an exponentially increasing function. In Section 4 we consider the consequences of changing the mechanism of pathogenesis by altering the term for parasite-induced mortality. We find that while these changes do not affect the within-host dynamics of parasites, they can dramatically alter the level of virulence at which the total transmission of parasites is maximized.

2. Basic model

We briefly describe a simple model for the within-host dynamics of microparasite infections of vertebrate hosts (for details see Antia et al., 1994; Ganusov et al., 2002). The model assumes the following:

1. Infection is initiated by a small dose of parasite $P(0)$ which grows exponentially at the rate r in the absence of the specific immune response.
2. The parasite, $P(t)$, kills the host if its density exceeds a lethal density D.
3. The specific immune response, $X(t)$, is generated by clonal expansion from a population of $X(0)$ precursors at the rate $\frac{sP(t)}{k+P(t)}$.
4. The specific immune response clears the parasite at the rate $hX(t)$.
5. Because we consider only acute infections (i.e., the parasite is cleared) we do not consider the subsequent contraction of the immune response.
6. The rate of transmission of the parasite, $\zeta[P(t)]$, is directly proportional to its density within the host, i.e. $\zeta[P(t)] = P(t)$.

With these assumptions the equations describing the within-host dynamics of the parasite and immune response are:

$$\frac{dP(t)}{dt} = P(t)(r - hX(t)) \quad \text{if } P(t) < D, \tag{2}$$

$$P(t) = 0 \quad \text{if } P(t) \geqslant D, \tag{3}$$

$$\frac{dX(t)}{dt} = \frac{sX(t)P(t)}{k + P(t)}. \tag{4}$$

The total transmission of the parasite over the course of acute infection (of duration Δ), $l(r)$, is

$$l(r) = \int_0^{\Delta} \zeta[P(t)]\, dt = \int_0^{\Delta} P(t)\, dt. \tag{5}$$

In Fig. 1A we show the dynamics of the infection for parasites with different growth rates. In Fig. 1B we show how the total transmission, $l(r)$, depends on the growth rate, r, of the parasite. We see that slowly growing parasites are cleared before they reach high density, and thus achieve relatively little total transmission. Parasites with an intermediate growth rate, r^*, which allows them to reach a maximum density just short of the lethal density before being cleared by the immune response are able to generate the maximum total transmission. Faster growing parasites, which reach the lethal density D, kill the host rapidly and this limits the total transmission of the parasite. These results suggest that evolution will select parasites with an intermediate growth rate.

The model is not able to describe intermediate levels of virulence in a satisfactory manner. This is because all infections are identical and thus either all hosts survive or all hosts die following infection. We note that the virulence measured in terms of the case mortality caused by the evolved parasite is equal to zero. However, an infinitesimal increase in the growth rate from the optimal level will result in the parasite killing all hosts (i.e., having a case mortality equal to 1), and a substantial decline in the total transmission at $r > r^*$ (which we term the cost of killing the host).

This problem can be resolved by introducing stochastic heterogeneity in the host population, and similar results are obtained if we introduce heterogeneity in the any of the parameters (Ganusov et al., 2002). In Fig. 1C we show how introducing heterogeneity in the lethal density D, results in intermediate levels of virulence (as measured by the case mortality) of the evolved parasite. We find that the level of virulence increases with increasing levels of host heterogeneity.

3. Changing the term for transmission

There are some experimental data suggesting that the rate of transmission of parasites from an infected host, $\zeta(P)$, is positively correlated with the density of parasite within the host, P (Fenner et al., 1956; Schulman, 1967; Taylor and Read, 1997; Pedraza et al., 1999; Quinn et al.,

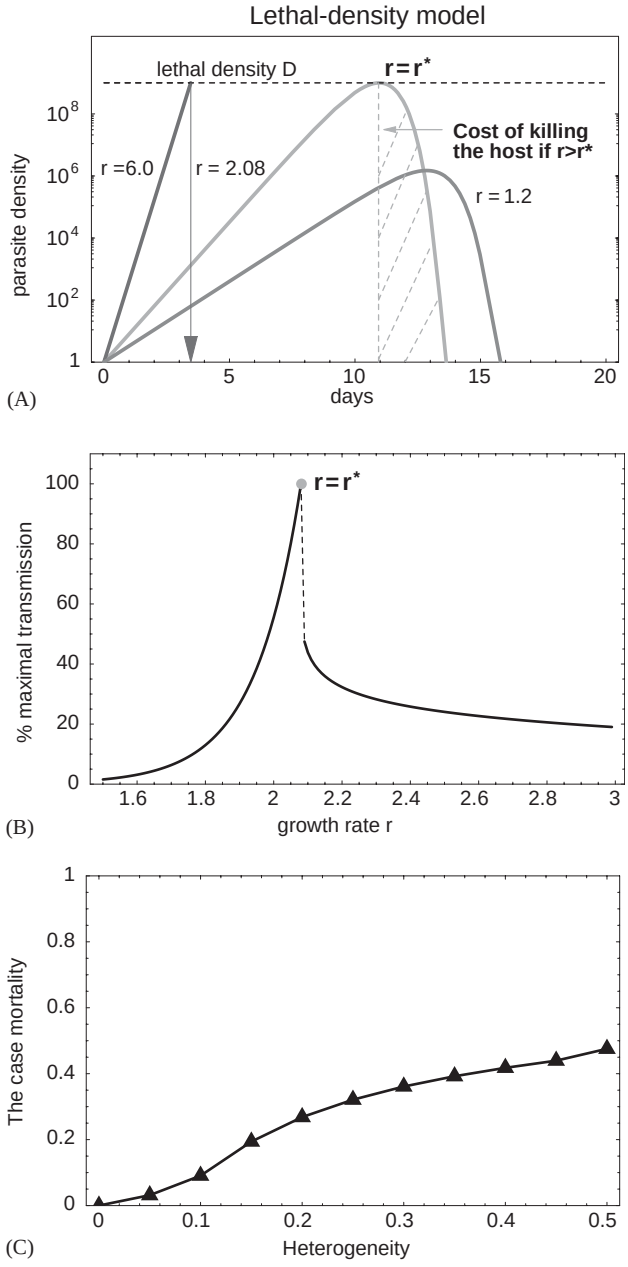

Fig. 1. The basic model for the evolution of microparasites. Panel (A) shows the within-host dynamics of parasites with different growth rates. Panel (B) shows the total transmission of parasites over the course of acute infection as a function of the growth rate. The dot at $r = r^*$ denotes the optimal parasite. Panel (C) shows the virulence (the case mortality) of the optimal parasite depends on the degree of heterogeneity. Heterogeneity is described by the coefficient of variation ($\mathrm{CV} = \sqrt{\text{variance}}/\text{mean}$) in the gamma distribution chosen for the lethal density (D). Parameters used for simulations: $P(0) = 1$, $X(0) = 1$, $h = 10^{-3}$, $k = 10^3$, $s = 1$, $D = 10^9$.

2000). However, the functional form of the term for the rate of transmission has not been quantitatively determined, and furthermore is likely to differ for different infections.

In the earlier model, we chose the simplest possible term, letting $\zeta(P)$ be linearly dependent on P. In this section we consider the consequences of changing $\zeta(P)$ to a function which increases slower than linearly as well as one which increases faster than linearly with increases in P. A slower than linear rate of increase in $\zeta(P)$ with P corresponds to a biological situation where the transmission rate saturates at high parasite densities. A faster than linear increase in $\zeta(P)$ with P corresponds to a biological situation where cooperative effects are needed for parasite transmission.

In the first case, when the transmission rate increases slower than linearly with increases in P, we let $\zeta(P)$ be a simple saturating function

$$\zeta(P) = \frac{P}{1 + P/\theta}, \tag{6}$$

where θ is the parasite density at which the transmission rate is half its maximum value. Biologically we expect that $\theta \gg P(0)$.

In the second case, when the rate of transmission increases faster than linearly, we let the transmission rate be proportional to the square of the parasite density:

$$\zeta(P) = P^2. \tag{7}$$

We call these two functions which describe the rate of transmission as a function of the within-host parasite density as saturating and squared transmission functions, respectively. We note that there could be more complex functions for the transmission rate which increase faster than linearly at low densities and saturate at high densities.

In Fig. 2A we show the dynamics of the infection for parasites with different growth rates. We see that, as might be expected, changing the function describing the transmission rate does not alter the within-host dynamics of infection (plots in Figs. 1A and 2A are identical). In Fig. 2B we show how the total transmission, $l(r)$, depends on the growth rate, r, of the parasite for the saturating and squared transmission functions. In order to facilitate comparisons we plot the value for the total transmission as a percent of the maximum transmission. We notice that the growth rate r^* of the parasite at which the total transmission is maximum is not altered by these changes in the function describing the transmission rate. When the rate of transmission is a saturating function we find that the peak in the plot of the total transmission as a function of the growth rate becomes broader. When the rate of transmission is a squared function we find that the peak in the plot of total transmission as a function of the growth rate becomes narrower.

In Fig. 2C we show how virulence of the optimal parasite (measured by the case mortality) changes with the degree of host heterogeneity. We find that for a given level of host heterogeneity, parasites with a saturating transmission function evolve lower virulence and para-

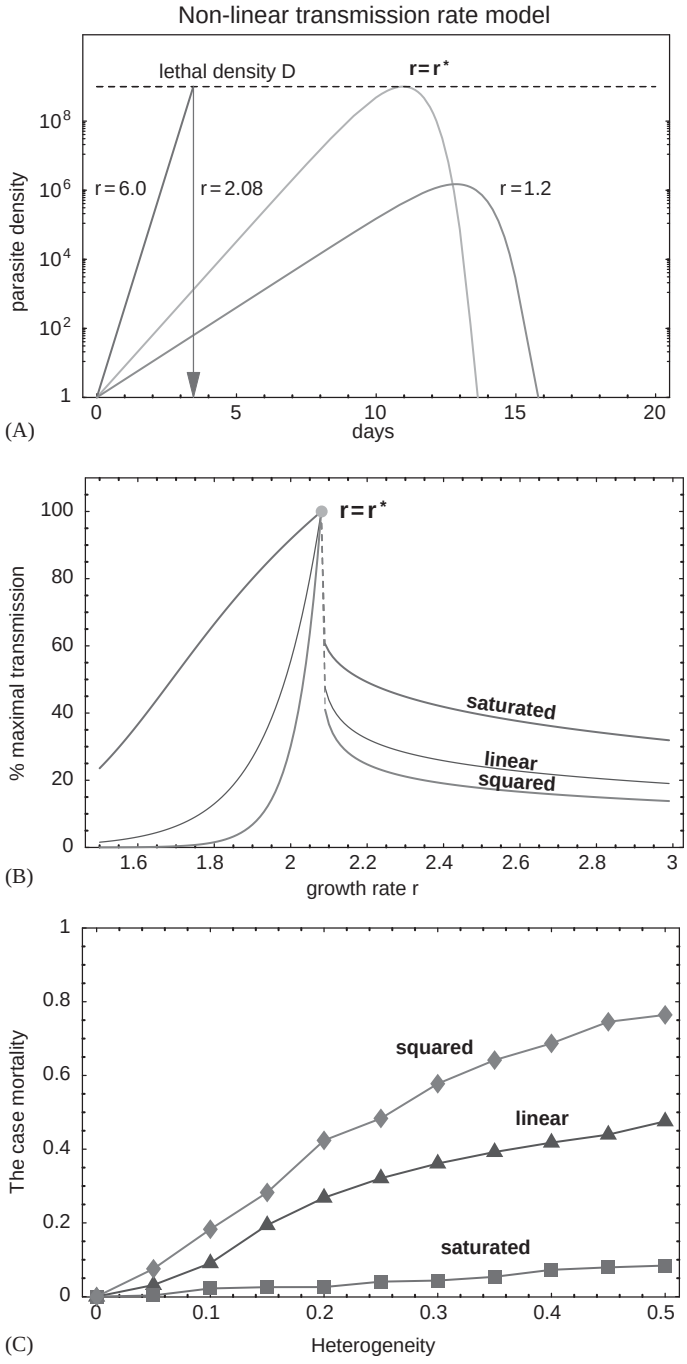

Fig. 2. Consequences of changing the transmission function (the function describing the rate of transmission as a function of the within-host density of the parasite). Linear function: $\zeta(P) = P$, saturating function: $\zeta(P) = \frac{P}{1+P/\theta}$, "square" function: $\zeta(P) = P^2$. Panel (A) shows that the within-host dynamics of parasites with different growth rates is not affected by the changes in the transmission function. Panel (B) shows the total transmission of parasites (normalized with respect to the maximum transmission) as a function of the growth rate of the parasite, for the different transmission functions. Panel (C) shows the virulence (case mortality) of the optimal parasite as a function of the degree of host heterogeneity for the different transmission functions. Heterogeneity is described by the coefficient of variation ($\mathrm{CV} = \sqrt{\mathrm{variance}}/\mathrm{mean}$) in the gamma distribution chosen for the lethal density (D). Parameters are the same as in Fig. 1 and $\theta = 10^7$.

sites with a squared transmission function evolve higher virulence when compared to parasites with a linear transmission rate. At high levels of heterogeneity, differences in the function describing the transmission rate can result in substantial differences in the level of virulence, as measured by the case mortality. This result occurs because of the shape of the plot of $l(r)$ vs. r. In the case of the "saturating" transmission function, as heterogeneity increases, the parasite obtains more total transmission if it errs on the side of having a slower

growth rate compared with r^*. The converse holds in the case of the "squared" transmission function.

4. Changing the term for pathogenesis

In the basic model pathogenesis was introduced by having a lethal parasite density, D. We assumed that the parasite kills infected hosts when it reaches this density within the host. There are many other mechanisms by which the parasite can induce pathogenesis. In this section we consider the consequences of changing the term for parasite-induced pathogenesis from lethal density to resource depletion (Marsh and Snow, 1997). In the resource depletion model, we assume that the parasite consumes a resource within the host, and this can cause the infected host to die if the level of resource falls below a threshold value. We call these two models the lethal density model and the resource depletion model.

We use a chemostat-type model for the resource, R (Pirt, 1975). Resource is generated at the rate $dR(0)$, and has a background turnover rate d. We assume that the parasite's growth rate is dependent on the consumption of the resource at the per capita rate $rR/(c+R)$ (Monod, 1949), and conversion efficiency y. Pathogenesis is introduced by assuming that the parasite kills the host if the resource density falls below some critical value $R_d < R(0)$. The terms for the immune response and transmission rate remain unchanged from the earlier model (i.e., Eqs. (4) and (5)). The rates of change in the density of resource, $R(t)$, and parasite, $P(t)$, are thus given by the equations:

$$\frac{dR(t)}{dt} = d(R(0) - R(t)) - y^{-1}\frac{rR(t)P(t)}{c+R(t)}, \tag{8}$$

$$\frac{dP(t)}{dt} = \frac{rR(t)P(t)}{c+R(t)} - hX(t)P(t) \quad \text{if } R(t) > R_d, \tag{9}$$

$$P(t) = 0 \quad \text{if } R(t) \leqslant R_d. \tag{10}$$

For simplicity, we consider the case when the rate of the resource turnover is slow in comparison with the time scale of an acute infection (i.e., $d = 0$), and parasite growth is not resource limited (i.e., $R_d > c$). A more comprehensive discussion of the other possibilities is presented in Appendix B.

In Fig. 3A we show the dynamics of the infection for parasites with different growth rates in the resource depletion model. To facilitate comparisons we choose R_d such as the optimal growth rate in this model in the absence of host heterogeneity is the same as in the lethal density model $r = r^* = 2.08$. We see that the within-host dynamics of infection are not substantially changed when the mechanism of pathogenesis is changed from lethal density to resource depletion. More detailed analysis revealed that when the growth rate is slightly greater than the optimal value (i.e., $r = r^* + \varepsilon$, where ε is small) the parasite depletes the resource when it has been almost cleared. Consequently, there is only a minimal

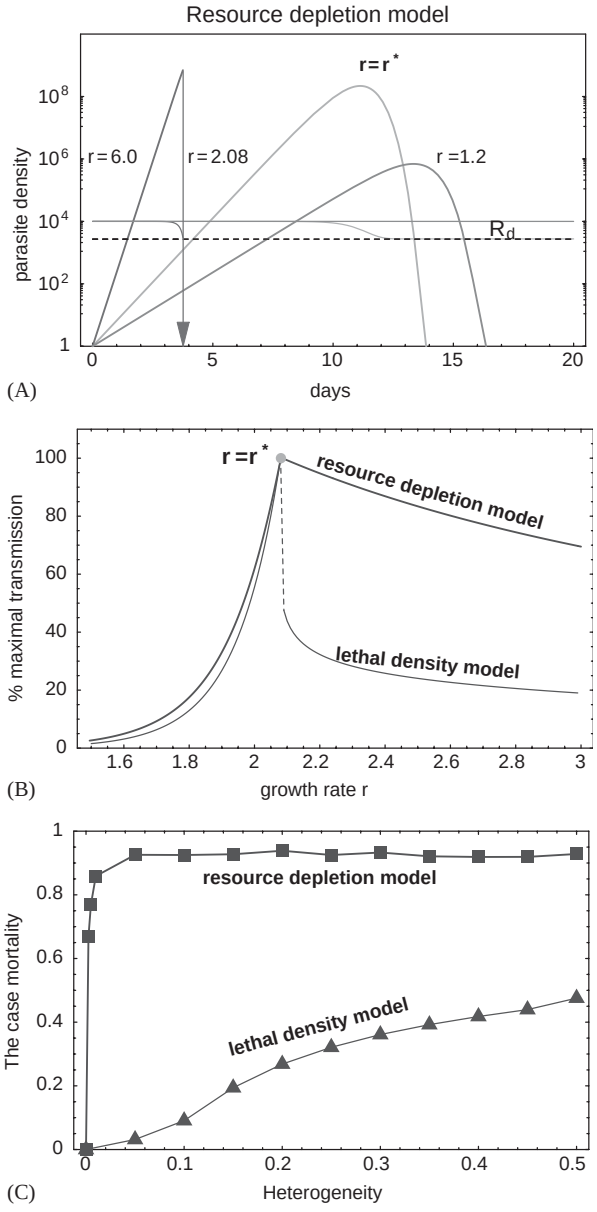

Fig. 3. Consequences of changing the mechanism of pathogenesis from a lethal density to resource depletion. Panel (A) shows the within-host dynamics of parasites (thick lines) and resource (thin lines) for parasites with different growth rates. Panel (B) shows the total transmission of parasites (normalized with respect to the maximum transmission) as a function of the growth rate of the parasite for the lethal density and resource depletion models. Panel (C) shows the virulence (case mortality) of the optimal parasite as a function of the degree of host heterogeneity for the lethal density and resource depletion models. Heterogeneity is described by the coefficient of variation ($CV = \sqrt{variance}/mean$) in the gamma distribution chosen for the lethal density, D, or minimum resource density, R_d. Parameters used for simulations are the same as in Fig. 1 and $R(0) = 10^4$, $c = 10^3$, $y = 10^5$, $R_d = 2.7 \times 10^3$, $d = 0$.

loss of transmission due to killing the host (in comparison with the large cost of killing the host in the lethal density model described earlier). This is reflected in Fig. 3B; we show how the (normalized) total transmission, $l(r)$, depends on the growth rate, r, of the parasite. We see that the major change introduced by this model occurs when the growth rate, r, exceeds optimal growth rate, r^* (i.e., when $r>r^*$). In this regime the resource depletion model gives a more gradual decrease in the total transmission with increasing growth rate r than the earlier lethal density model.

In Fig. 3C we show how virulence of the optimal parasite (measured by the case mortality) changes with the degree of host heterogeneity (introduced in the lethal density D in the lethal density model and the critical resource density R_d in the resource depletion model). In the lethal density model, the case mortality increases slowly with increasing heterogeneity. In contrast, in the resource depletion model the case mortality increases very rapidly with increasing heterogeneity and then saturates. These results suggest that changing the mechanism of pathogenesis can substantially alter the virulence of an evolved parasite.

5. Discussion

There is a large body of literature on the evolution of parasite virulence and the reader is directed to excellent reviews on this subject (e.g., Bull, 1994; Frank, 1996; Ebert, 1999). The hypotheses for the observed virulence of parasites include the following. (i) The virulence of parasites may be coincidental (i.e., unrelated to their fitness; Levin and Bull, 1994). (ii) The virulence of parasites may arise as a consequence of the within-host competition resulting from high mutation rates, co- or superinfection (Frank, 1992; Bonhoeffer and Nowak, 1994; Nowak and May, 1994; May and Nowak, 1995; van Baalen and Sabelis, 1995; Mosquera and Adler, 1998). (iii) The virulence of parasites may arise as a consequence of their evolutionary adaptation to maximize their total transmission in the host population (Anderson and May, 1982). In this latter view, known as the adaptive framework, virulence arises as a consequence of the trade-offs between the transmission rate, host recovery rate, and virulence of the infection caused by the parasite. We also note that, in general, the evolution of the host in response to the parasite will result in the reduction of parasite virulence, possibly leading to a co-evolutionary arms-race between parasite and host (Gilchrist and Sasaki, 2002).

We have focused on the adaptive framework. Within this framework, a number of factors, including the route of parasite transmission (Ewald, 1983), host resistance (Gandon et al., 2001), and the interaction of the parasite and the host immune response (Antia et al., 1994), have been proposed to affect the optimal level of virulence.

In this paper, we used a model of the within-host dynamics of microparasites that cause acute infections in vertebrate hosts. Using this model we explored how changes in the rate of parasite transmission from infected hosts and mechanisms of parasite-induced pathogenesis affect the level of virulence to which a parasite evolves. Our results suggest that changing the transmission rate or mechanism of pathogenesis can result in dramatic changes in this optimal level of virulence of the parasite.

What are the implications of our results for understanding the evolution of virulence of parasites? Our major result is that predicting the optimal level of virulence of a parasite will require a detailed quantitative understanding of the interaction of the parasite and its host. These could include the mode of parasite transmission (direct, indirect, vector-borne, etc.), how the rate of transmission depends on the parasite density, the interactions between the parasite and non-specific immunity (Antia and Koella, 1994; Pilyugin and Antia, 2000; Kerr and McFadden, 2002), the mechanisms of generation of specific immune responses (Kaech et al., 2002; Antia et al., 2003), intra-host competition (Leung and Forbes, 1998), different mechanisms of parasite-induced pathogenesis (target cell vs. resource depletion, toxin production, etc), and host heterogeneity (Ebert and Hamilton, 1996; Regoes et al., 2000; Ganusov et al., 2002). Furthermore, our results strongly suggest that in the absence of such an understanding it may be difficult to predict the extent to which changes in a single parameter will change the optimal level of virulence of a parasite.

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Appendix A. Calculating the average total transmission and case mortality

For a parasite with the growth rate r we calculate two parameters: (1) the average total transmission of the

parasite in a heterogeneous host population, $L(r)$, representing fitness of the parasite, and (2) the case mortality caused by the parasite, $M(r)$, representing virulence of the parasite. To describe host heterogeneity, we use a gamma distribution of the lethal density D. Then $f(D)\,dD$ is a probability of choosing a host with the lethal density in the range $(D, D+dD)$.

The average total transmission of a parasite with the growth rate r in a heterogeneous host population characterized by the probability distribution $f(D)$ is

$$L(r) = \int_0^\infty l(r,D) f(D)\,dD. \tag{A.1}$$

where $l(r,D)$ is the total transmission of a parasite with the growth rate r infecting a host with the lethal density D ($l(r,D)$ is given in Eq. (5)). We numerically calculate the integral in Eq. (A.1) by evaluating $l(r,D)f(D)$ for every D at fixed r.

We find the optimal growth rate of the parasite r_{opt} at which the average total transmission $L(r)$ reaches its maximum using a "finding a minimum" algorithm (*brent*) from the Numerical Recipes (http://www.library.cornell.edu/nr/bookcpdf/c10-2.pdf).

The case mortality is the probability that a randomly chosen host will die following infection. To estimate the case mortality of a parasite with the growth rate r, we first calculate the maximum density, $P_{max}(r)$, that the parasite can reach during the acute infection (assuming no host mortality, i.e., $D=\infty$). The case mortality is simply the fraction of hosts which have their lethal densities below $P_{max}(r)$:

$$M(r) = \int_0^{P_{max}(r)} f(D)\,dD. \tag{A.2}$$

Appendix B. The evolution of extracellular microparasites depleting host resources during the acute infection

In the main text we restricted our analysis of the resource depletion model to a particular case when the rate of the resource turnover is zero, i.e., $d=0$. Here we investigate how the rate of the resource turnover, d, affects the evolution of extracellular parasites that kill their hosts by depleting the host resource during acute infection.

We find that there are two critical parameters in the model which determine the within-host dynamics of parasites. These are the rate of the resource turnover, d, and the critical resource density, R_d. The last parameter affects the dynamics of parasites differently depending on whether $R_d \gg c$ or $R_d \ll c$, where c is the half-saturation constant for the growth rate of the parasite (see Eq. (9)). In all cases the parasite that depletes the host resource until the density R_d and does not kill the host achieves maximal total transmission.

When $R_d \gg c$, the parasite grows approximately exponentially at the maximum rate r until it either kills the host or is controlled and cleared by the immune response. As the rate of the resource turnover, d, increases, we find that (1) the optimal growth rate of the parasite increases at all else being equal, and (2) the minimal density of the resource during the acute infection becomes inversely correlated with the peak of parasitemia (Fig. 4A). Both changes are intuitively obvious. As the rate of resource turnover increases, the minimal resource density during the infection increases; therefore, in order for the parasite to deplete the resource to R_d, it must increase its growth rate. At high rates of resource turnover the resource becomes a "fast" variable, changes in which are rapidly adjusted to the changes in the parasite density.

The parasites with the growth rate just infinitesimally higher than the optimal will pay much higher cost of killing the host (i.e., loss in the total transmission) when the rate of resource turnover is high (Fig. 4C). As a consequence we find that the optimal level of virulence, measured by the case mortality, monotonically decreases with the increasing rate of the resource turnover for a given level of heterogeneity in R_d (Fig. 4E).

When $R_d \ll c$ the within-host dynamics of the parasite and resource remain similar to the previous case except the case when the resource turnover is high. When d is high, parasite density saturates as the resource density falls below c (Fig. 4B). The growth rate at which the total transmission of the parasite is maximal increases with the increasing rate of resource turnover. The cost of killing the host is also high when the resource turnover is high (Fig. 4D).

However, in contrast with the previous case, the optimal level of virulence of the parasite is not strictly a decreasing function of the turnover rate d (Fig. 4F); even though the general trend is observed, at some intermediate turnover rates ($d = 10^{-1} - 5\times 10^{-1}$) the case mortality increases with the increasing turnover rate. There are two factors which lead to changes in the case mortality. First, as the rate of resource turnover increases, the case mortality of a parasite with the fixed growth rate r decreases because the parasite depletes less resource (see Fig. 4A and B). On the other hand, an increase in the growth rate at fixed d will lead to a higher case morality because the parasite depletes the resource to a lower density. As the rate of resource turnover increases, the optimal growth rate increases, and as the result, the case mortality may change in either way (decrease or increase), depending on which of the changes (turnover rate vs. growth rate) has a greater impact. It seems that the general trend is nevertheless robust—when the resource turnover is high, the optimal level of virulence of the parasite is low and vice versa.

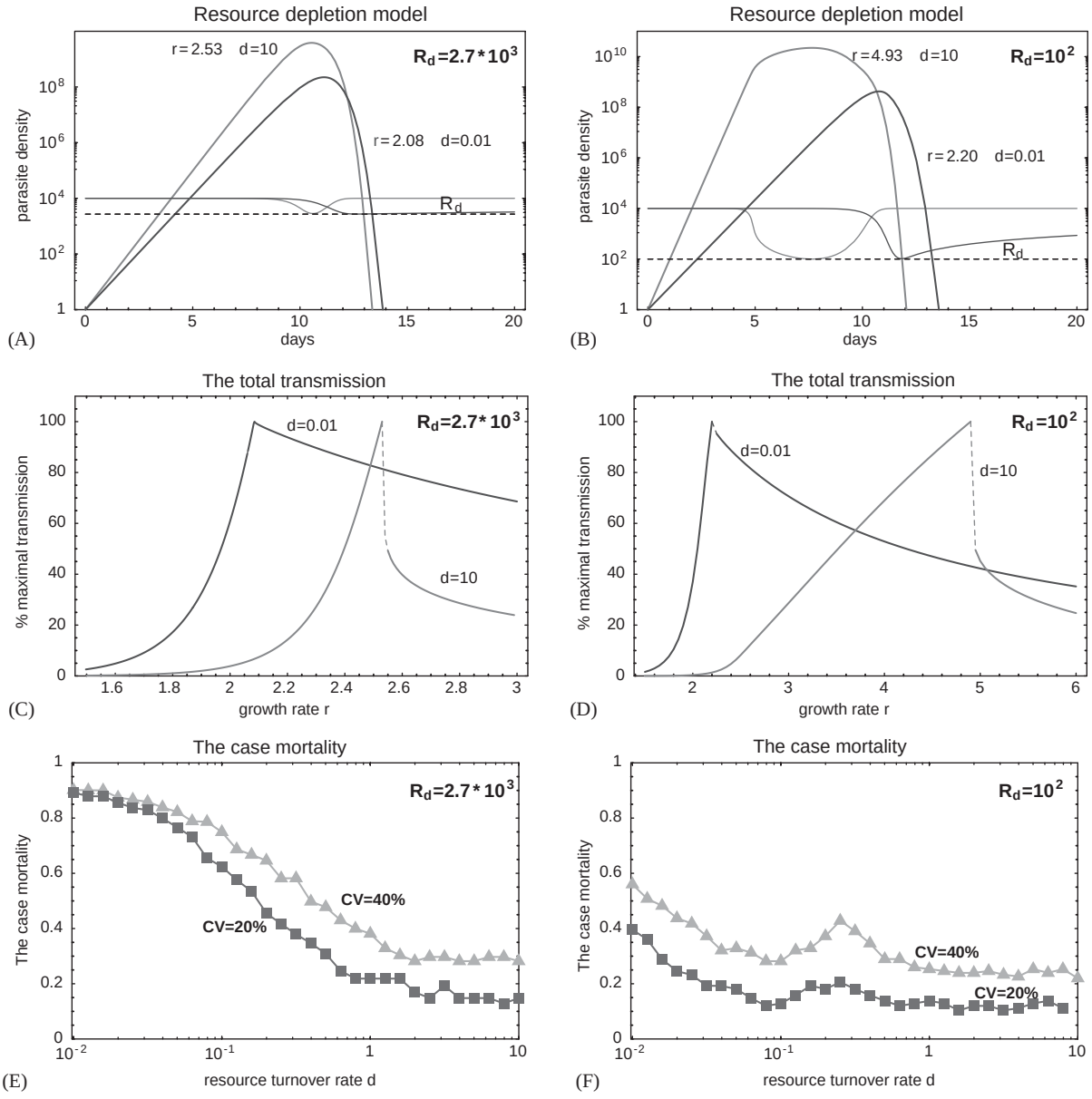

Fig. 4. The evolution of extracellular microparasites according to the resource depletion model in a heterogeneous host population. Panels (A,B) show the within-host dynamics of optimal parasites at different rates of resource turnover d when the minimal resource density is high (A, $R_d = 2.7 \times 10^3 \gg c$) and low (B, $R_d = 10^2 \ll c$). Thick lines—parasites, thin lines—resources, a dashed horizontal line denotes the minimal resource density R_d. Panels (C,D) show the total transmission of parasites (normalized with respect to the maximum transmission) over the course of acute infection as a function of the growth rate at high (C) and low (D) minimal resource density. The rate of the resource turnover is marked. Panels (E,F) show virulence (case mortality) of the optimal parasite as a function of the resource turnover rate when minimal resource density R_d is high (E) or low (F). Heterogeneity is described by the coefficient of variation ($CV = \sqrt{\text{variance}}/\text{mean}$) in the gamma distribution chosen for the minimal resource density R_d. Note that higher levels of host heterogeneity lead to higher case mortality in accordance with previous results. Parameters are the same as in Fig. 3 with $d > 0$.

These changes in the optimal level of parasite virulence with changes in the rate of resource turnover are not specific to heterogeneity in R_d; the same trend is observed when heterogeneity is introduced into the parameter k (see Eq. (4) and Fig. 5). Interestingly, with heterogeneity in k the case mortality decreases monotonically with the rate of resource turnover d even at $R_d \ll c$.

Explicit trade-offs. Previously we assumed that parasites evolve their growth rate r and that changes in the growth rate do not affect other parameters. However, we might expect that parasites that grow faster may utilize the resource with lower efficiency. What would happen if such a trade-off is explicitly introduced into the resource depletion model?

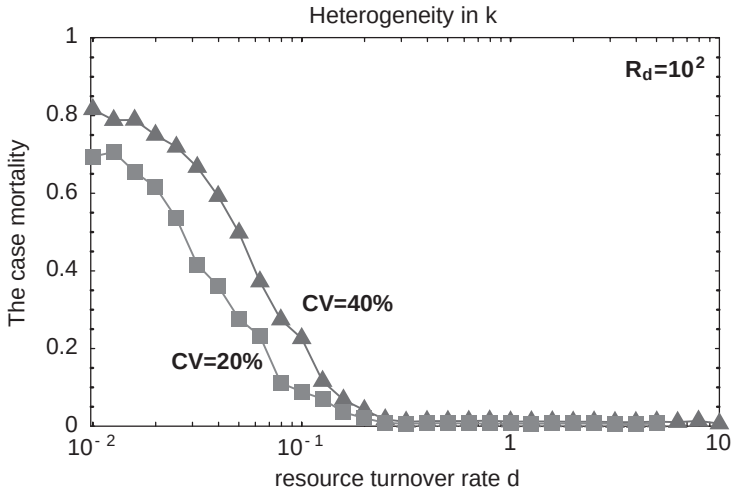

Fig. 5. Virulence (case mortality) of the optimal parasite as a function of the resource turnover rate when heterogeneity is described by a gamma distribution of k. Heterogeneity is described by the coefficient of variation ($\mathrm{CV} = \sqrt{\text{variance}}/\text{mean}$). Parameters are the same as in Fig. 3 except $R_d = 10^2$.

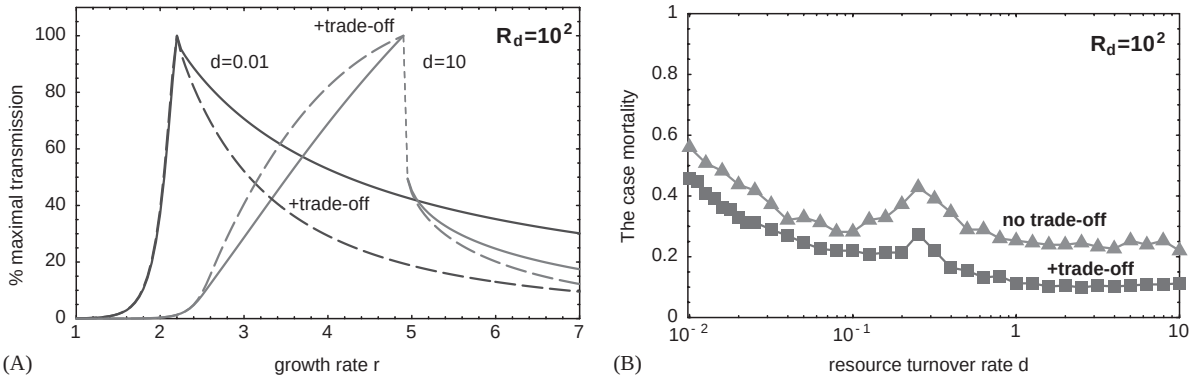

Fig. 6. The evolution of extracellular microparasites when there is a constrain (trade-off) on the efficiency of resource consumption y and the growth rate r. Panel (A) shows the total transmission of parasites (normalized with respect to the maximum transmission) over the course of acute infection as a function of the growth rate in the absence (solid lines) and presence (dashed lines) of the trade-off. The rate of the resource turnover is marked. Trade-off functions used are $y = 4.9 \times 10^5/r$ for $d = 10$ and $y = 2.2 \times 10^5/r$ for $d = 0.01$ (parameters are chosen to provide peaks of the total transmission at the same growth rates at two rates of resource turnover). Panel (B) shows virulence (case mortality) of the optimal parasite as a function of the resource turnover rate in the presence or absence of the trade-off. Heterogeneity is described by a gamma distribution in the minimal resource density R_d ($\mathrm{CV} = 40\%$, $\overline{R_d} = 10^2$). For a linear trade-off ($y = 10^5(10 - r)$) similar results were obtained (not shown). Parameters are the same as in Fig. 4.

We tested two different types of the trade-off: linear ($y(r) = y_0(10 - r)$) and hyperbolic ($y(r) = y_0/r$), and the qualitative trend seems to be independent of the particular trade-off type (not shown). The difference between the maximum total transmission (at $r = r^*$) and total transmissions of parasites with smaller growth rate ($r < r^*$) is lower when there is trade-off (Fig. 6A; the difference is obvious when $d = 10$ but is too small to be seen for $d = 0.01$). Parasites with higher growth rates ($r > r^*$) have a lower total transmission when there is a trade-off. Introducing heterogeneity in R_d we find that the trade-off between efficiency of resource consumption and the growth rate generally leads to selection of less virulent parasites (Fig. 6B); the exact nature of the trade-off (for example, linear vs. hyperbolic) also influences the exact level of virulence parasites evolve (not shown).

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